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Long-Term Valve Performance of TAVR and SAVR

A Report From the PARTNER I Trial

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the long-term performance of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) through longitudinal echocardiographic analysis.

BACKGROUND The long-term performance of the SAPIEN TAVR is not well-described. Therefore, we examined the hemodynamic and valvular profile of the SAPIEN TAVR over 5 years.

METHODS All patients receiving TAVR or SAVR with first post-implant (FPI) and 5-year echoes were analyzed for aortic valve (AV) peak velocity, AV mean gradient, AV area, peak left ventricular (LV) outflow tract and in-stent velocities, Doppler velocity index, aortic regurgitation (AR), LV mass index, stroke volume index, and cardiac index. The FPI and 5-year data were compared using a paired *t* test or McNemar's analyses.

RESULTS There were 86 TAVR and 48 SAVR patients with paired FPI and 5-year echocardiograms. Baseline characteristics were similar between groups. The AV area did not change significantly 5 years after TAVR ($p = 0.35$). The AV mean gradient also remained stable: 11.5 ± 5.4 mm Hg at FPI to 11.0 ± 6.3 mm Hg at 5 years ($p = 0.41$). In contrast, the peak AV and LV outflow tract velocities decreased ($p = 0.03$ and $p = 0.008$, respectively), as did in-stent velocity ($p = 0.015$). Correspondingly, the TAVR Doppler velocity index was unchanged ($p = 0.07$). Among TAVR patients, there was no change in total AR ($p = 0.40$), transvalvular AR ($p = 0.37$), or paravalvular AR ($p = 0.26$). Stroke volume index and cardiac index remained stable ($p = 0.16$ and $p = 0.25$, respectively). However, there was a significant regression of LV mass index ($p < 0.0001$). The longitudinal evaluation among SAVR patients revealed similar trends. There was a low rate of adverse events among TAVR and SAVR patients alive at 5 years.

CONCLUSIONS Longitudinal assessment of the PARTNER (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial) I trial demonstrates that valve performance and cardiac hemodynamics are stable after implantation in both SAPIEN TAVR and SAVR in patients alive at 5 years. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial [PARTNER]; NCT00530894) (J Am Coll Cardiol Img 2017;10:15–25) © 2017 by the American College of Cardiology Foundation.

The PARTNER (Placement of AoRTic TraNscathetER Valve Trial) I trial demonstrated that transcatheter aortic valve replacement (TAVR) was associated with similar clinical outcomes when compared with surgical aortic valve replacement (SAVR) among patients with severe symptomatic aortic stenosis (AS) and high surgical risk (1). As a result, percutaneous valvular intervention was

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

AV = aortic valve

AVA = aortic valve area

BSA = body surface area

DVI = Doppler velocity index

FPI = first post-implant

LV = left ventricle

LVOT = left ventricular outflow tract

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TVI = time velocity integral

shown to be a viable alternative to surgical valve replacement. After 5 years of follow-up, the clinical outcomes for TAVR and SAVR patients has remained similar (2). We hypothesize that the long-term performance of TAVR will similarly remain stable; however, data on the long-term durability, structural integrity, and valvular hemodynamics of TAVR, as well as the resultant changes in cardiac structure and function after percutaneous aortic valve (AV) implantation, remain scarce.

Echocardiography is the recommended imaging modality for the assessment of prosthetic valve function and extended follow-up (3). The long-term function of surgically implanted prosthetic AVs has been monitored traditionally by quantitative parameters such as peak velocity, mean gradient, valve area, and Doppler velocity index (DVI) (3). However, the SAPIEN transcatheter AV (Edwards Lifesciences, Irvine, California) has a unique hemodynamic profile characterized by in-stent flow acceleration (4). This in-stent, pre-cusp flow acceleration is not accounted for with traditional methods of assessing prosthetic valve function, nor is it known if this novel hemodynamic profile remains stable or changes over time.

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Furthermore, long-term valve performance is of particular interest in light of recent concerns over reduced AV leaflet motion and possible subclinical thrombosis in both TAVR and bioprosthetic SAVR (5–7). Therefore, in this study we examined the serial changes in valve performance and cardiac structure and function over 5 years of follow-up in high-risk patients treated for severe AS with either SAPIEN TAVR or SAVR.

METHODS

STUDY DESIGN AND PATIENT SELECTION. The study design of the PARTNER I trial has been published previously (1,8). Briefly, the PARTNER I trial incorporated 2 parallel prospective, randomized, controlled clinical trials consisting of either high-risk surgical candidates (mortality ≥15%) randomized to SAPIEN TAVR or SAVR for the treatment of severe AS (cohort A) or inoperable severe AS patients randomized to SAPIEN TAVR versus standard therapy (cohort B). Patients in the PARTNER I trial had serial echocardiograms performed at baseline (before valve replacement), 7 days, 30 days, 6 months, 1 year, and then annually through 5 years.

This current analysis evaluates the longitudinal changes in valve performance, as well as cardiac structure and function, among patients undergoing SAVR in cohort A and patients receiving TAVR as part of either cohort A or B of the PARTNER I trial. Patients had to have a first post-implant (FPI) and a 5-year echocardiogram to be included in the primary analysis. FPI was defined as the first available echocardiogram performed at either 7 or 30 days after valve replacement. Patients who underwent AV re-intervention after initial replacement or died before 5 years of follow-up were excluded from the primary analysis. Patients who died before 5 years were included in a secondary analysis if they had 2 consecutive echocardiograms preceding death that were adequate for image interpretation. All analyses were performed on paired data for each patient to assess the gradient of change over time for each echocardiographic parameter.

ECHOCARDIOGRAPHIC CORE LABORATORY ANALYSIS. All 2-dimensional transthoracic echocardiograms were analyzed by an independent core laboratory at Duke Clinical Research Institute. Echocardiographic image quality was ensured by the use of a detailed acquisition protocol, site qualification and training with quarterly quality feedback, and retraining of sites with unacceptable image quality. Image interpretation was standardized through group and individual training, regular reproducibility testing, and the use of a detailed analysis protocol based on current guidelines and standardized endpoint definitions (3,9,10).

Valve performance was evaluated by serial assessment of AV peak velocity, AV peak gradient, AV mean gradient, aortic valve area (AVA), AVA indexed

Canada; and has received grant support from Edwards Lifesciences. Dr. Svensson holds equity in Cardiosolution and Valvexchange; and intellectual property with Postthorax. Dr. Kodali has received grants from Edwards Lifesciences and Medtronic; is a member of the PARTNER Trial Executive Committee; and holds equity in Thubrikar Aortic Valve, Inc. Dr. Szeto has received consulting fees/honoraria from Microinterventional Devices. Dr. Makkar has received grants from Edwards Lifesciences and St. Jude Medical; is a consultant for Abbott Vascular, Cordis, and Medtronic; and holds equity in Entourage Medical. Drs. Mack, Svensson, and Leon have received travel reimbursements from Edwards Lifesciences related to their work as unpaid members of the PARTNER Trial Executive Committee. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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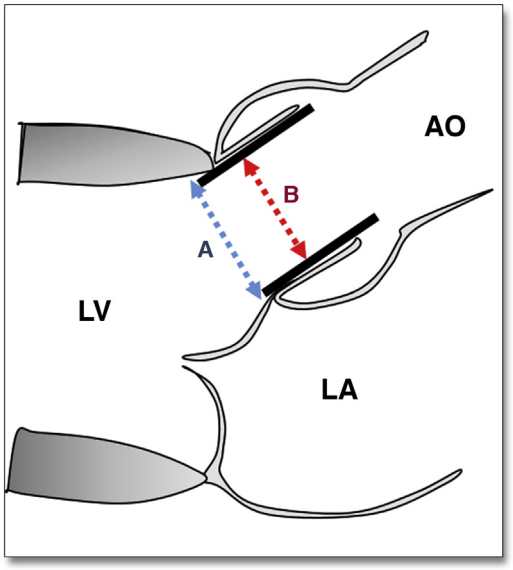
for body surface area (BSA), pre-stent peak velocity in the left ventricular outflow tract (LVOT), in-stent (pre-leaflet) peak velocity, time velocity integrals (TVI), DVI using transvalvular flow and either TVI_{LVOT} or $TVI_{instent}$, and total, transvalvular, and paravalvular aortic regurgitation (AR). The LVOT diameter and in-stent diameter were measured using a lagging-edge to leading-edge technique, parallel to the AV plane in the parasternal long axis view (**Figure 1**) (9,11). The mean AV gradient and TVIs were measured by tracing Doppler velocity profiles. The AVA was calculated by the continuity equation using TVIs. The DVI_{LVOT} was derived by dividing TVI_{LVOT} by TVI_{AV} and the $DVI_{instent}$ by dividing $TVI_{instent}$ by TVI_{AV}. The severity of AR was assessed in all relevant views using color and spectral Doppler echocardiography and graded according to recommendations from the American Society of Echocardiography and the Valve Academic Research Consortium-2 (3,10,12).

Cardiac hemodynamics and left ventricular (LV) structure and function were assessed using stroke volume, ejection fraction, LV mass, cardiac output, and cardiac index. Stroke volume was calculated as the LVOT area measured just proximal to the stent edge multiplied by the pulsed wave Doppler TVI_{LVOT} and indexed to BSA. The ejection fraction was measured by the biplane Simpson method, as permitted by image quality, or estimated based on visual assessment. The LV mass was determined using the formula recommended by the American Society of Echocardiography and indexed to BSA (13). The hemodynamic parameter of cardiac output was calculated by multiplying the stroke volume by the heart rate and then divided by BSA to derive the cardiac index.

A secondary analysis was performed among patients with consecutive echocardiograms before death, which evaluated for an increase in mean gradient of >10 mm Hg and/or a decrease in DVI <0.25 and/or the development of new severe AR. These parameters were selected because of their known association with valve dysfunction and adverse clinical events (3,10).

REPRODUCIBILITY. All sonographers and interpreting cardiologists adhered to established best practice standards for echocardiography core laboratories, which included reproducibility testing for AVA, peak and mean gradients, biplane ejection fraction, and transvalvular and paravalvular AR (14). Intrareader and inter-reader reproducibility for these echocardiographic parameters has been reported previously and demonstrated high reproducibility across all readers for continuous variables (intraclass correlation coefficient: 0.89 to 0.99) and moderate to high agreement for categorical variables (kappa statistic: 0.58 to 0.85) (9).

FIGURE 1 Left Ventricular Outflow Tract and In-Stent Diameter Measurements



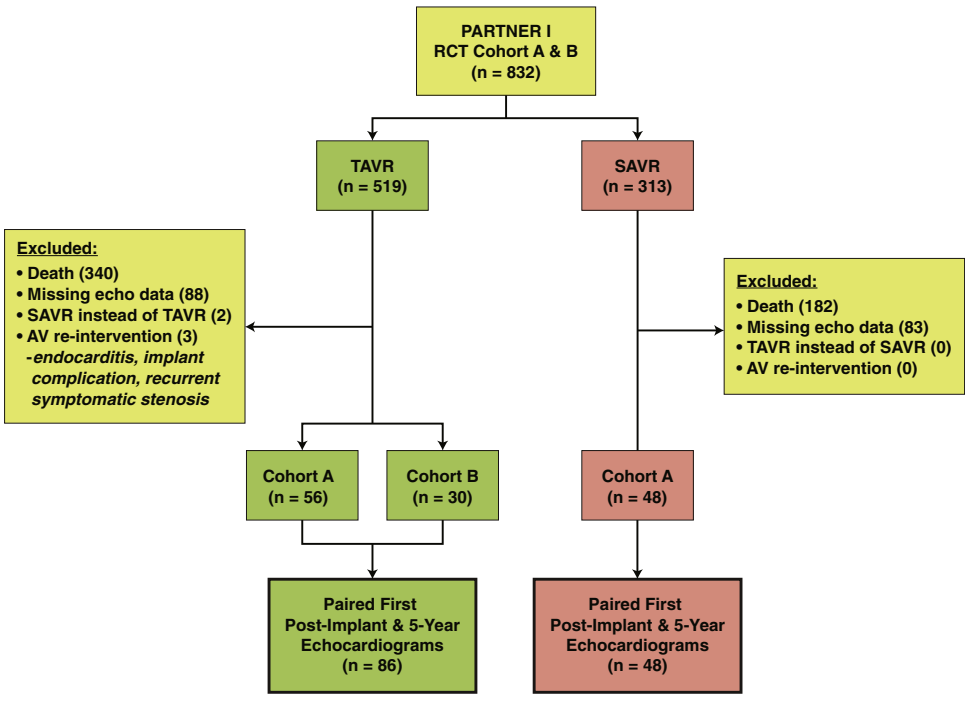
Left ventricular outflow tract diameter **(A)** and in-stent diameter **(B)** were measured using a lagging edge to leading edge technique parallel to the aortic valve plane in the parasternal long-axis view. Ao = aorta; LA = left atrium; LV = left ventricle.

STATISTICAL ANALYSIS. Echocardiographic and statistical analyses were performed on an as-treated basis depending on the actual valve implant patients received (TAVR or SAVR) in accordance with the PARTNER I trial protocol. Comparisons between the 2 independent groups were performed by a paired *t* test or chi-square test, as appropriate. Variables were compared between FPI and 5-year time points using the paired *t* test or McNemar test for continuous and categorical variables, respectively. Continuous variables are presented as mean ± SD. Data are based on a data extraction date of December 19, 2014. For all analyses, statistical significance was defined at an alpha level of <0.05. All statistical calculations were carried out using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Over the course of the PARTNER I trial, 313 patients received SAVR and 519 underwent TAVR (344 in cohort A and 175 in cohort B). Of these, 86 TAVR and 48 SAVR patients had paired FPI and 5-year echocardiograms

FIGURE 2 CONSORT Diagram



Patients included in the TAVR and SAVR groups and reasons for exclusion. AV = aortic valve; PARTNER = Placement of AoRTic TraNscathetER Valve Trial; RCT = randomized control trial; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

and comprised the study population for the primary analysis (Figure 2). Baseline characteristics among TAVR and SAVR patients with and without FPI and 5-year data are in Online Tables 1 and 2.

The baseline clinical characteristics between cohort A SAVR patients and the combined cohort A and B TAVR patients were similar except for a higher proportion of hypertension and peripheral vascular disease among SAVR patients (Table 1). On baseline echocardiography, the valve groups were similar in AV mean gradient, AVA, AVA index, AR and MR severity, LV mass index, stroke volume index, ejection fraction, and cardiac index (Table 1). There were no differences between cohort A and B TAVR patients in the combined TAVR arm, except for a greater frequency of moderate or severe AR among TAVR B patients (Online Table 3).

There were 3 patients still alive at 5 years who had required AV re-intervention previously and were, therefore, excluded from this analysis. The first developed fungal endocarditis requiring surgical valve replacement. The second patient underwent a seemingly successful percutaneous TAVR; however, the following day this patient was found to have severe AR due to a nonfunctioning leaflet attributed to an implant complication. This patient received a valve-in-valve procedure that same day and had no further complications. The third patient had a successful TAVR but 4 years later presented with heart failure and was found to have recurrent severe AS and moderate to severe AR. This patient was also treated with a valve-in-valve procedure.

LONG-TERM VALVE PERFORMANCE. Five years after patients received SAPIEN TAVR, the AVA and AVA index were not significantly different from FPI ($p = 0.35$, $p = 0.44$, and $p = 0.56$, respectively) (Table 2, Figure 3A). Similarly, the AV mean gradient did not change significantly: from 11.5 ± 5.4 mm Hg at FPI to 11.0 ± 6.3 mm Hg at 5 years ($p = 0.41$) (Figure 3B). Furthermore, when the absolute change in mean gradient from FPI to 5 years was evaluated for each patient, the majority (78 TAVR patients) had a change of <10 mm Hg (Figure 3C). In contrast, the peak AV and LVOT velocities decreased significantly ($p = 0.03$ and $p = 0.008$, respectively), as did in-stent velocity ($p = 0.015$). Correspondingly, TAVR DVI using LVOT TVI or in-stent TVI were unchanged.

Among SAVR patients, AVA and AVA index also remained stable after 5 years of follow-up (Table 3,

TABLE 1 Baseline Characteristics of TAVR and SAVR Patients

	TAVR (n = 86)	SAVR (n = 48)	p Value
Clinical characteristics			
Age, yrs	82.7 ± 7.4	82.2 ± 6.4	0.70
Male	41 (47.7)	27 (56.3)	0.34
Body surface area, m^2	1.8 ± 0.3	1.9 ± 0.2	0.27
Hypertension	74 (86.0)	48 (100)	0.004
Hyperlipidemia	72 (83.7)	45 (93.8)	0.09
Smoking	43 (50.0)	25 (52.1)	0.82
Peripheral vascular disease	22 (25.6)	23 (47.9)	0.009
Renal insufficiency (Cr ≥2)	17 (19.8)	8 (16.7)	0.66
Coronary artery disease	63 (73.3)	40 (83.3)	0.18
Prior myocardial infarction	21 (24.7)	18 (37.5)	0.12
STS score	10.7 ± 3.5	11.4 ± 3.0	0.26
NYHA functional class III/IV	79 (91.9)	47 (97.9)	0.26
Prior balloon valvuloplasty	13 (15.1)	6 (12.5)	0.68
Echocardiographic characteristics			
AV mean gradient, mm Hg	49.5 ± 17.8	45.2 ± 13.4	0.12
AV peak gradient, mm Hg	81.6 ± 28.2	76.1 ± 22.4	0.22
AV peak velocity, cm/s	445.8 ± 76.9	432.8 ± 58.9	0.28
AV area, cm^2	0.64 ± 0.2	0.68 ± 0.2	0.23
AV area index, cm^2/m^2	0.35 ± 0.1	0.37 ± 0.1	0.27
Doppler velocity index (by LVOT TVI)	0.19 ± 0.1	0.21 ± 0.1	0.13
Moderate or severe AR	14 (17.1)	6 (12.8)	0.52
Moderate or severe MR	22 (26.8)	6 (13.0)	0.07
LV mass, g	284.2 ± 90.0	276.0 ± 81.5	0.62
LV mass index, g/m^2	156.6 ± 41.9	149.8 ± 43.7	0.41
Ejection fraction, %	51.9 ± 13.2	53.2 ± 13.5	0.57
Doppler stroke volume, ml	67.1 ± 22.1	70.2 ± 16.3	0.37
Doppler stroke volume index, ml/m^2	37.1 ± 11.3	38.6 ± 10.8	0.46
Cardiac output, l/min	4.7 ± 1.5	5.1 ± 1.4	0.18
Cardiac index, $l/min/m^2$	2.6 ± 0.8	2.8 ± 0.9	0.27

Values are mean ± SD or n (%).

AR = aortic regurgitation; AV = aortic valve; Cr = creatinine; LV = left ventricle; LVOT = left ventricular outflow tract; MR = mitral regurgitation; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TVI = time-velocity index.

TABLE 2 Longitudinal Valve and Hemodynamic Performance of TAVR

	TAVR (n = 86)			
	First Post-Implant	5-Year	Δ (95% CI)	p Value
Valve performance				
AV peak velocity, cm/s	227.5 ± 53.5	213.4 ± 50.0	-14.1 (-26.8 to -1.4)	0.03
AV mean gradient, mm Hg	11.5 ± 5.4	11.0 ± 6.3	-0.6 (-2.02 to 0.84)	0.41
LVOT peak velocity, cm/s	108.6 ± 24.7	99.4 ± 25.7	-9.2 (-15.9 to -2.5)	0.008
LVOT TVI, cm	21.5 ± 6.2	21.9 ± 6.2	0.4 (-1.1 to 1.9)	0.59
In-stent peak velocity, cm/s	173.5 ± 33.6	153.3 ± 25.5	-20.2 (-36.1 to -4.3)	0.015
In-stent TVI, cm	35.3 ± 8.0	32.9 ± 6.6	-2.4 (-6.41 to 1.62)	0.23
DVI with LVOT TVI	0.53 ± 0.2	0.49 ± 0.1	-0.04 (-0.08 to 0.00)	0.07
DVI with in-stent TVI	0.84 ± 0.2	0.76 ± 0.2	-0.08 (-0.17 to 0.01)	0.09
AV area, cm^2	1.62 ± 0.5	1.56 ± 0.5	-0.06 (-0.18 to 0.07)	0.35
AV area index, cm^2/m^2	0.88 ± 0.3	0.86 ± 0.3	-0.03 (-0.1 to 0.04)	0.44
Cardiac structure and function				
Doppler stroke volume, ml	66.0 ± 18.0	69.7 ± 22.4	3.7 (-1.2 to 8.5)	0.13
Doppler SV index, ml/m^2	36.8 ± 10.9	38.8 ± 12.6	1.9 (-0.8 to 4.7)	0.16
Ejection fraction, %	56.1 ± 10.4	54.6 ± 9.2	-1.5 (-3.7 to 0.7)	0.17
Cardiac output, l/min	4.7 ± 1.3	5.0 ± 1.6	0.3 (-0.1 to 0.6)	0.14
Cardiac index, $l/min/m^2$	2.6 ± 0.8	2.8 ± 0.9	0.1 (-0.1 to 0.4)	0.25
LV mass index, g/m^2	151.1 ± 35.3	120.7 ± 37.5	-30.4 (-39.4 to -21.4)	<0.0001

Values are mean ± SD unless otherwise noted. Δ indicates difference between first post-implant and 5-year mean values.

CI = confidence interval; DVI = Doppler velocity index; SV = stroke volume; other abbreviations as in Table 1.

Figure 4A). The mean gradient did not change over time (**Figure 4B**); only 2 patients had an absolute change in mean gradient of >10 mm Hg from FPI to 5 years after surgical valve replacement (**Figure 4C**). Similar to TAVR, there was a significant decrease in THE AV peak velocity and LVOT peak velocity, and no change in DVI.

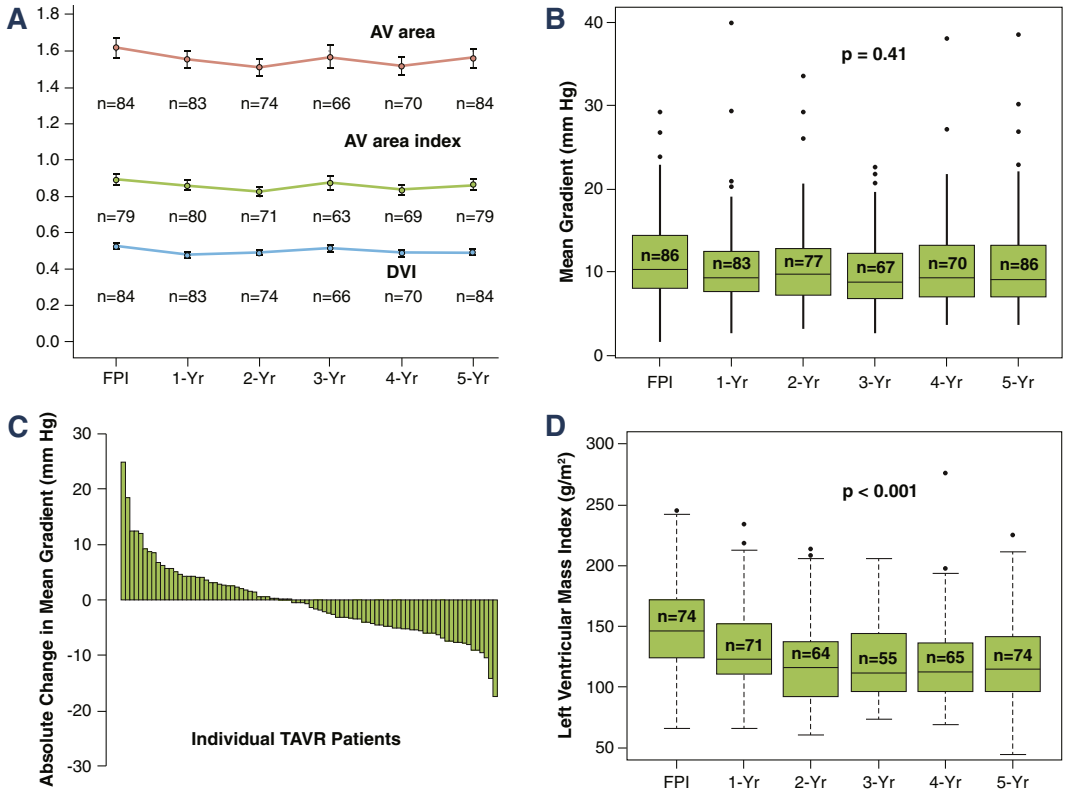
LONG-TERM VALVE REGURGITATION. Total, transvalvular, and paravalvular AR were not different at 5 years compared with post-implant values in patients undergoing TAVR ($p = 0.40$, $p = 0.37$, and $p = 0.26$, respectively). In particular, no patients in this analysis had severe AR at any post-implant time point. Furthermore, there was no increase in mild or greater paravalvular AR among patients alive at 5 years, but rather a nonsignificant decrease was seen (**Figure 5A**).

Overall, SAVR patients had less AR but, similar to TAVR patients, there was no severe AR at any post-implant time point and no change in total, transvalvular, or paravalvular AR from FPI to 5 years ($p > 0.99$ for all) (**Figure 5B**). Mitral regurgitation remained stable over time in both TAVR ($p = 0.58$) and SAVR ($p = 0.29$) patients alive at 5 years.

LONG-TERM CARDIAC STRUCTURE AND FUNCTION. The stroke volume and ejection fraction did not change from FPI to 5 years in either TAVR or SAVR patients (**Tables 2** and **3**). Similarly, cardiac output and cardiac index remained stable over time in both groups. However, there was a significant regression in LV mass index among both TAVR and SAVR patients ($p < 0.0001$ for both groups) (**Figures 3D** and **4D**).

LONG-TERM CLINICAL OUTCOMES. There was a low rate of adverse clinical outcomes at 5 years among TAVR and SAVR patients (**Table 4**). Among patients with an absolute increase in mean gradient of >10 mm Hg, which has been shown previously to be significant clinically and correlated with adverse clinical outcomes (10). Of the 5 TAVR patients, 2 had a repeat hospitalization and 1 experienced a transient ischemic attack in the follow-up period. The 1 SAVR patient with

FIGURE 3 Valve Hemodynamics and Left Ventricular Mass Index of TAVR



(A) Trend in AV area, AV area index, and Doppler velocity index (DVI) from first post-implant (FPI) through 5 years in TAVR patients with paired echocardiograms. **(B)** Box plots of the mean aortic valve gradient from FPI through 5 years. **(C)** The absolute change in mean gradient from FPI to 5 years for each patient. **(D)** Box plots of the left ventricular mass index from FPI through 5 years. Box plot center line is the median with whisker lengths extending 1.5 times the interquartile range above Q3 and below Q1. The p values represent paired 2-sample analysis of results at FPI and 5 years. Abbreviations as in Figure 2.

an absolute increase in the mean gradient of >10 mm Hg required repeat hospitalization (Table 5).

SECONDARY ANALYSES. Although patients who died before 5 years of follow-up were excluded from the primary analysis, we conducted a secondary analysis to determine whether any patients had sudden worsening of valve performance before they died. There were 340 patients (207 TAVR, 104 SAVR) who had ≥2 consecutive echocardiograms before they died. Among these patients, 8 TAVR and 1 SAVR had an increase of >10 mm Hg on consecutive echocardiograms before they died (5 TAVR and 1 SAVR in year 1; 1 TAVR and 0 SAVR in year 2; 2 TAVR and 0 SAVR in year 3; and 0 TAVR and 0 SAVR in year 4). Seven (6 TAVR and 1 SAVR) had a DVI decrease to <0.25 before death: 5 TAVR and 1 SAVR in year 1; 0 TAVR and 0 SAVR in year 2; 1 TAVR and 0 SAVR in year 3; and 0 TAVR and 0 SAVR in year 4. Only 3 TAVR and 0 SAVR patients developed new severe AR on the echocardiograms preceding death (2 TAVR and 0 SAVR in year 1; 1 TAVR and 0 SAVR in year 2; 0 TAVR and 0 SAVR in year 3; and 0 TAVR and 0 SAVR in year 4).

DISCUSSION

The PARTNER I trial is the first large, randomized trial evaluating TAVR and SAVR patients treated for severe symptomatic AS and showed comparable outcomes (1,2). In this study, we used centrally analyzed, paired echocardiographic data to evaluate the long-term valve performance and cardiac hemodynamics of TAVR and SAVR patients over the 5 years after valve intervention Whereas previous reports have examined the difference in overall group mean hemodynamics between TAVR and SAVR at

specific post-implantation time points (1,2,15), this study used individual patients' paired echocardiographic analyses at FPI and 5 years to detail the temporal trend in valvular and hemodynamic performance over time for TAVR and SAVR. This longitudinal hemodynamic assessment revealed that, similar to SAVR, the valve performance of the SAPIEN TAVR remains stable after implantation in individual patients alive at 5 years.

VALVE PERFORMANCE. The flow-independent parameters of AVA, AVA index, and DVI did not change in patients alive at 5 years after TAVR or SAVR, which underscores the importance of a serial evaluation of flow-independent parameters for the long-term monitoring of valve performance. In contrast, the flow-dependent parameters of AV peak velocity and peak gradient significantly decreased over time among both TAVR and SAVR patients, which may have been influenced by changes in heart rate, intravascular volume status, and myocardial loading conditions. Similarly, the mean gradient tended to be lower at 5 years than at FPI, but this difference was not statistically significant in either valve group.

The stability of the flow-independent parameters over time is particularly important in light of the unique hemodynamic profile of the SAPIEN TAVR characterized by in-stent flow acceleration (4), which is not present in surgically implanted bioprosthetic AVs. This study confirms that there is an increase in peak velocity from the LVOT location (pre-stent) to the pre-leaflet in-stent location: 108.6 ± 24.7 cm/s and 173.5 ± 33.6 cm/s, respectively, most likely due to the smaller in-stent diameter relative to the LVOT, as has been reported previously. This velocity step-up was similar in magnitude at FPI (65 cm/s) and 5 years (54 cm/s). Correspondingly, whether the DVI was calculated using the LVOT TVI or the in-stent TVI, this ratio remained stable over time, which supports good long-term durability and freedom from structural valve deterioration. However, to ensure accuracy it is critical that the same pulse wave Doppler location, whether it be LVOT or in-stent, be used consistently in serial TAVR evaluations of valve performance.

Recently, concerns about reduced AV leaflet motion and possible subclinical valve thrombosis in severe AS patients treated with transcatheter or surgically implanted bioprosthetic valves have resulted in increased utilization of transesophageal echocardiography and cardiac computed tomography for the evaluation of bioprosthetic valve performance (5,7). Unfortunately, these higher resolution imaging modalities were not required in the protocol for the PARTNER I trial, and therefore were not incorporated into the central core laboratory analysis for the study. However, in a recent report by Makkar et al. (5), valvular parameters obtained by transthoracic echocardiography showed that mean gradients were not different between patients with reduced leaflet motion and those with normal leaflet motion at hospital discharge, 30 days, or 6 months. This suggests that reduced AV leaflet motion as a result of subclinical valve thrombosis may not be detectable by transthoracic echocardiographic evaluation alone, and therefore the prevalence of subclinical valve thrombosis could not be evaluated in the present study.

In contrast, clinically significant, symptomatic valvular dysfunction due to overt valve thrombosis, endocarditis, or severe patient-prosthesis mismatch may be characterized by a marked elevation in mean AV gradients (16–19). Among those patients included in the current study, we evaluated the absolute change in mean gradient from FPI to 5 years for each TAVR and SAVR patient and found that the vast majority had a change of <10 mm Hg over long-term follow-up. However, there were 8 TAVR and 2 SAVR patients who had an absolute change in the mean gradient of >10 mm Hg. Of the TAVR patients, 5 had an increase of over 10 mm Hg and 3 had a decrease of 10 mm Hg between FPI and 5 years. Three of 5 TAVR patients who demonstrated an increase in the mean gradient during this time had an adverse clinical event, either transient

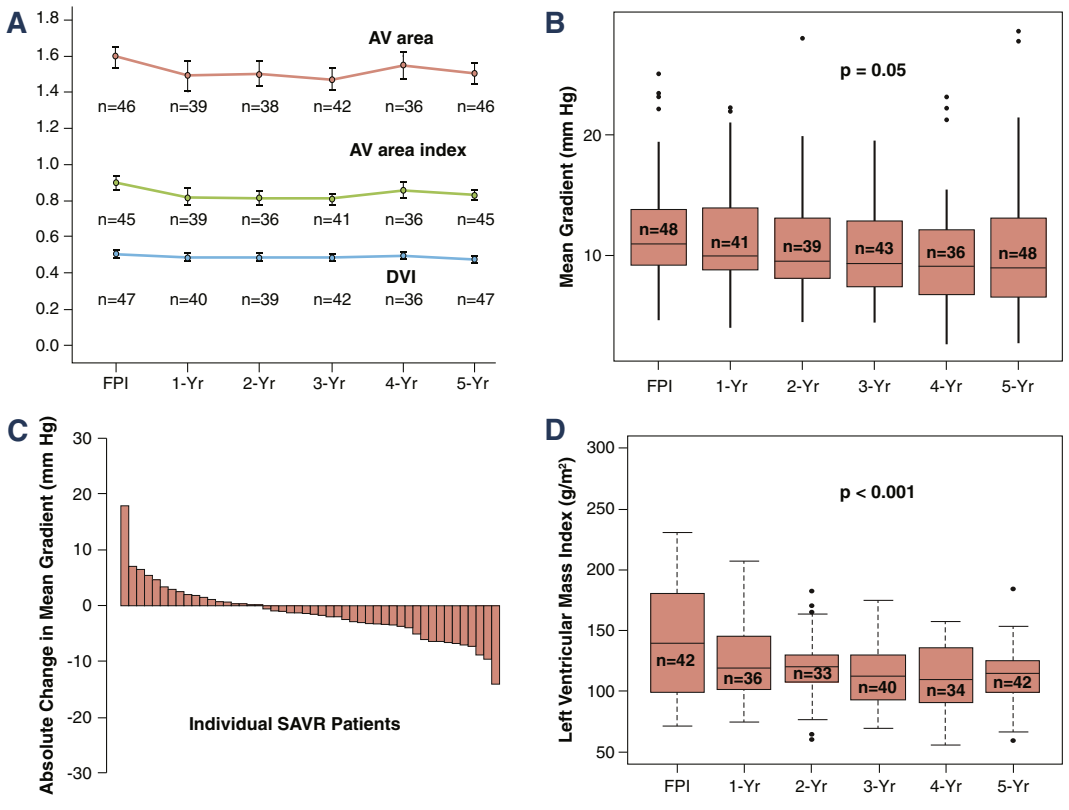
TABLE 3 Longitudinal Valve and Hemodynamic Performance of SAVR

	SAVR (n = 48)			
	First Post-Implant	5-Year	Δ (95% CI)	p Value
Valve performance				
AV peak velocity, cm/s	232.0 ± 46.7	208.7 ± 45.0	-23.3 (-35.3 to -11.2)	0.0003
AV mean gradient, mm Hg	12.1 ± 5.0	10.6 ± 5.5	-1.5 (-2.9 to 0.0)	0.051
LVOT peak velocity, cm/s	109.1 ± 24.5	93.5 ± 22.1	-15.6 (-25.1 to -6.1)	0.0019
LVOT TVI, cm	19.7 ± 4.8	21.1 ± 5.8	1.36 (-0.6 to 3.3)	0.17
In-stent peak velocity, cm/s	N/A	N/A	N/A	N/A
In-stent TVI, cm	N/A	N/A	N/A	N/A
DVI with LVOT TVI	0.50 ± 0.1	0.48 ± 0.1	-0.02 (-0.07 to 0.02)	0.27
DVI with in-stent TVI	N/A	N/A	N/A	N/A
AV area, cm^2	1.59 ± 0.4	1.51 ± 0.4	-0.08 (-0.24 to 0.08)	0.31
AV area index, cm^2/m^2	0.9 ± 0.3	0.84 ± 0.2	-0.06 (-0.15 to 0.03)	0.19
Cardiac structure and function				
Doppler stroke volume, ml	61.1 ± 17.2	66.1 ± 18.8	4.5 (-2.3 to 11.2)	0.19
Doppler SV index, ml/m^2	33.7 ± 10.2	35.5 ± 9.0	1.9 (-1.7 to 5.4)	0.30
Ejection fraction, %	53.0 ± 11.3	55.3 ± 9.1	2.3 (-0.4 to 5.0)	0.09
Cardiac output, l/min	4.6 ± 1.7	4.8 ± 1.9	0.3 (-0.2 to 0.8)	0.28
Cardiac index, $l/min/m^2$	2.6 ± 1.0	2.6 ± 0.9	0.03 (-0.2 to 0.3)	0.78
LV mass index, g/m^2	142.8 ± 43.9	114.0 ± 25.8	-28.9 (-40.4 to -17.3)	<0.0001

Values are mean ± SD unless otherwise noted. Δ indicates true difference between paired first post-implant and 5-year values.

Abbreviations as in Tables 1 and 2.

FIGURE 4 Valve Hemodynamics and Left Ventricular Mass Index of SAVR



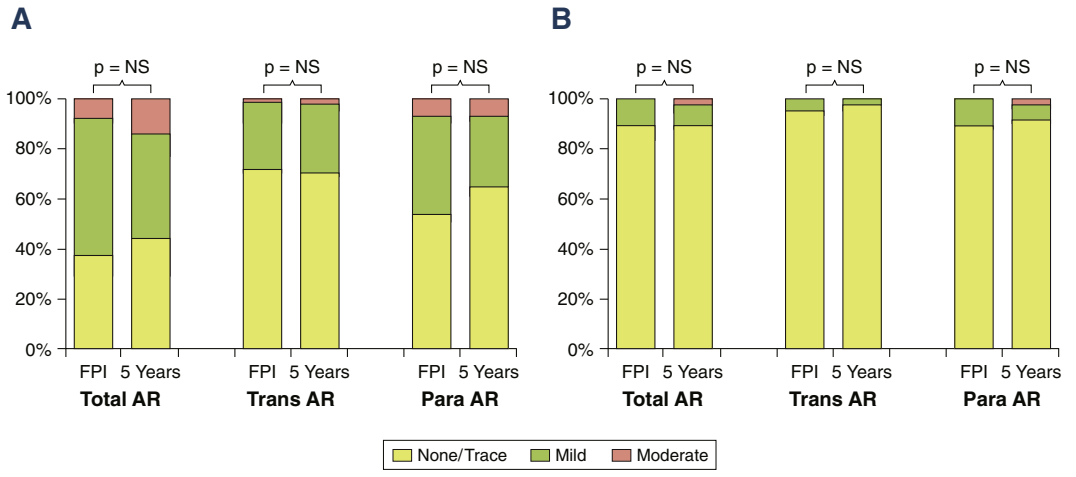
(A) Trend in AV area, AV area index, and DVI from FPI through 5 years in SAVR patients with paired echocardiograms. **(B)** Box plots of the mean aortic valve gradient from FPI through 5 years. **(C)** Absolute change in mean gradient from FPI to 5 years for each patient. **(D)** Box plots of the left ventricular mass index from FPI through 5 years. Box plot center line is the median with whisker lengths extending 1.5 times the interquartile range above Q3 and below Q1. The p values represent paired 2-sample analysis of results at FPI and 5 years. Abbreviations as in Figures 2 and 3.

ischemic attack or repeat hospitalization, whereas, only 1 of 3 with a decrease in the mean gradient had an adverse clinical outcome (repeat hospitalization). Among the 2 SAVR patients, one had an increase in mean gradient (11.0 to 28.5 mm Hg) and subsequently had a re-hospitalization, but the other SAVR patient had a decrease in mean gradient of 14 mm Hg (from 23.4 to 9.4 mm Hg) and had no adverse clinical events in the follow-up period. The incidence of an increased gradient and the high frequency of events associated with it are congruent with other recent reports (5,20). Although infrequent and far from definitive given our small numbers and selected population, this series of patients supports the suggestion that an increase in mean gradient of >10 mm Hg may be a marker of worse clinical outcomes in patients who have had AV replacement performed either percutaneously or surgically.

Given the association between an increase in the mean gradient of >10 mm Hg and adverse outcomes, we assessed for this degree of change among patients who died in the follow-up period but had consecutive echocardiograms before death. We also examined these serial studies for a decrease in DVI to <0.25 and the development of new severe AR. Reassuringly, the occurrence of these findings was rare even among patients who died in the follow-up period.

Similar to SAVR patients, those patients alive 5 years after TAVR demonstrated that the severity of total, transvalvular, and paravalvular AR remained stable over time. Importantly, there was no increase in mild or greater paravalvular AR among patients alive at 5 years, but rather a nonsignificant decrease was seen. The absence of progressive AR, particularly paravalvular AR, is supportive of good long-term valve durability and reassuring given that previous studies have shown that the development of even mild

FIGURE 5 Longitudinal Trend in Aortic Regurgitation Among TAVR and SAVR Patients



(A) The severity of total, transvalvular, and paravalvular aortic regurgitation (AR) for TAVR patients at FPI and 5 years. **(B)** The severity of total, transvalvular and paravalvular AR for SAVR patients at FPI and 5 years. Abbreviations as in Figures 2 and 3.

paravalvular regurgitation following SAVR or TAVR is associated with increased mortality (15,21–23).

CARDIAC HEMODYNAMICS. There were no changes in stroke volume, stroke volume index, cardiac output, or cardiac index from FPI to 5 years in TAVR and SAVR patients, but a positive trend was seen in all parameters in both groups. Interestingly, a significant regression in the LV mass index was seen among both TAVR and SAVR patients. Prior work has demonstrated that early regression of LV mass index in the 30 days after TAVR is associated with lower hospitalization rates and a trend toward better quality of life at 1 year (24). The current study illustrates that LV mass continues to decrease during long-term follow-up and was significantly reduced 5 years following TAVR and SAVR; however, the impact of this LV mass regression on clinical outcomes was not assessed in this study.

CLINICAL OUTCOMES. Similar to the overall 5-year PARTNER I cohort A results (2), this study found that, among SAVR and TAVR patients alive at 5 years with paired echocardiographic analyses, there was a low rate of adverse clinical outcomes, including repeat hospitalization, myocardial infarction, stroke, or transient ischemic attack. The comparable incidence of adverse clinical outcomes between the 2 valve groups parallels the comparable valvular and hemodynamic performance between TAVR and SAVR over 5 years of follow-up.

Studies of the long-term durability of bioprosthetic SAVR have shown an estimated freedom from structural valve deterioration of 85 ± 0.4% after 10 years and 63 ± 3% after 15 years and re-operation rates of 12.1% at 15 years (25–27). Although extended follow-up is needed to confirm the valve integrity and durability for TAVR, these 5-year data show parallel results for valve performance between SAVR and TAVR and, if a similar trajectory is maintained, would suggest that TAVR may have equivalent durability to SAVR over extended long-term follow-up.

TABLE 4 Clinical Outcomes at 5 years Among TAVR and SAVR Patients

	TAVR (n = 86)	SAVR (n = 48)
Stroke or TIA	8 (8.8)	4 (8.3)
Myocardial infarction	1 (1.1)	3 (6.3)
Repeat hospitalization	20 (22.2)	16 (33.3)

Values are n (%).
TIA = transient ischemic attack; other abbreviations as in Table 1.

TABLE 5 Annual Mean Gradients Among TAVR and SAVR Patients With an Absolute Increase of >10 mm Hg

	First Post-Implant	1-Year	2-Year	3-Year	4-Year	5-Year	Clinical Outcome
TAVR	8.1	20.3	29.2	22.6	13.9	20.1	Repeat hospitalization
TAVR	4.3	8.7	10.7	12.3	21.8	22.8	TIA
TAVR	9.7	16.2	N/A	19.7	19.6	22.2	Repeat hospitalization
TAVR	14.4	17.9	16.0	N/A	N/A	26.9	No adverse events
TAVR	13.6	40.0	19.2	21.8	38.1	38.5	No adverse events
SAVR	11.0	16.3	15.9	17.2	23.1	28.5	Repeat hospitalization

N/A = data not available; other abbreviations as in Tables 1 and 4.

Such evidence on the long-term durability of TAVR may be especially useful in supporting the use of TAVR technology in younger and lower risk patient populations. Previous work has highlighted the intermediate-term durability of SAPIEN TAVR after 2 years of follow-up (28). However, the current study is the first to demonstrate the long-term durability of the SAPIEN TAVR with valvular and hemodynamic performance comparable with SAVR.

STUDY LIMITATIONS. This study was derived from a high-risk population with multiple comorbidities and a high mortality rate, resulting in small numbers for long-term analysis that may be influenced by survival bias. Furthermore, baseline heterogeneity may have been introduced by combining cohort A and B TAVR patients, although this may actually be more reflective of current use of TAVR in clinical practice. All analyses were performed by an independent echocardiographic core laboratory that provided rigorous standardization and quality control of image analysis and demonstrated good reproducibility for categorical and continuous variables; however, even a limited amount of measurement variability could have introduced bias in this relatively small substudy population. Additionally, only 2-dimensional transthoracic echocardiography was used in the current study; it is possible that 3-dimensional transthoracic or transesophageal echocardiography or cardiac computed tomography may have demonstrated more nuanced differences over time. However, the similar clinical outcomes between the valve groups suggests that the stability of common transthoracic echocardiographic parameters in TAVR and SAVR patients is adequate for serial, long-term monitoring of valve performance and cardiac hemodynamics. Finally, although we cannot determine definitively whether hemodynamic deterioration contributed to any deaths given the limitation of protocolized annual echocardiograms, the secondary analysis was reassuring in that it showed that significant changes in valve performance were rare.

CONCLUSIONS

In contrast with previous studies that relied on site interpretations or reported only short- or intermediate-term follow-up on a subset of the PARTNER I trial, this study included the long-term, independently analyzed, paired echocardiographic analyses from high-risk patients undergoing either TAVR or SAVR for the treatment of severe, symptomatic AS. Significant changes in valve performance were rare, even among patients who died in the follow-up period. Flow-independent parameters of AVA, AVA index, and DVI did not change significantly over time and the severity of AR did not increase with either prosthesis type. Importantly, this study demonstrates that, among the high-risk patients alive at 5 years, the long-term valve performance and cardiac hemodynamics of both SAPIEN TAVR and SAVR are stable, suggesting that both valve types have good long-term durability and structural integrity.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The long-term valvular and hemodynamic performance of SAPIEN TAVR showed no changes in AV mean gradient, area or AR, whereas velocities decreased and cardiac index remained unchanged. Longitudinal evaluation among SAVR patients revealed similar trends. These results demonstrate good long-term durability of valve replacement in high-risk AS patients alive at 5 years, regardless of valve type.

TRANSLATIONAL OUTLOOK: Given the valvular and hemodynamic stability of SAPIEN TAVR up to 5 years after implantation in high-risk AS patients, consideration of this therapeutic intervention may be warranted in lower risk AS patients.

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KEY WORDS aortic stenosis, surgical aortic valve replacement, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this article.